

**REMARKS**

Applicants respectfully request reconsideration and withdrawal of the outstanding Office Action rejections in view of the foregoing amendments and following remarks.

Claims 10, 13, 40, and 46 have been amended. Claims 47 and 48 are new claims dependent from claims 10 and 13, respectively. No new subject matter has been added.

Claim 43 was objected to for being dependent from rejected claim 12. Claim 43 has been cancelled, and claim 12 has been amended to recite metastasizing colon, colorectal or breast cancer. Applicants direct the Examiner's attention to the attachment which includes data of the detection of MACC1 (7a5/prognostin) in breast cancer and blood plasma.

Claims 10-13 stand rejected under 35 USC § 112, first paragraph, where the Examiner does not find enablement for tumor diseases besides colon cancer. Claim 10 has been amended to limit diagnosis to colon, colorectal or breast cancer. Support for breast cancer diagnosis is provided in the attachment which shows MACC1 (7a5/prognostin) identified in breast cancer tumors.

Claims 10 and 13 have been amended to recite "bodily fluid" based on data presented in the attachment. Tumor derived transcripts of prognostin were identified in circulating blood plasma. Claims 11-13 are dependent from claim 10 and should be allowable based on the amendment to claim 10.

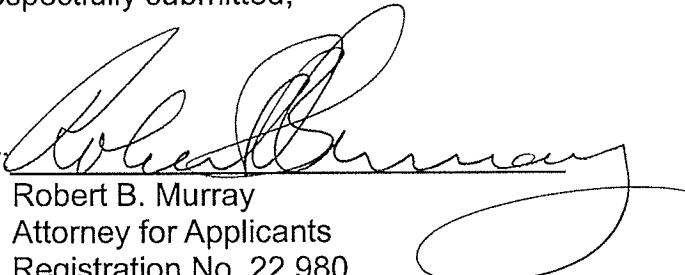
On page 4, paragraph 2 of the office action, the Examiner questions the manuscript figure (Supplemental Figure 1) submitted with the May 21, 2008 Response, in that the Examiner does not see a significant difference in Prognostin expression between primary and metastatic cancer cells. In response, applicants assert that elevated Prognostin levels are not merely found in metastases, but also in primary tumors with a high metastatic potential. The primary tumor cells in the figure are likely to produce metastases because Prognostin is highly expressed. Primary cells with low levels of Prognostin, as shown in Figures 2 and 4 of the specification, are less likely to produce metastases. Referring to Supplemental Figure 1 of the Response filed on May 21, 2008, compared to the low Prognostin levels in colon mucosa and normal liver cells, the elevated levels of Prognostin in primary tumor and liver metastases are indicative of cancer.

An extension of time of one month is respectfully requested to make this response timely. The required fee is to be charged to Deposit Account No. 02-2135. The Commissioner is hereby authorized to charge any additional fees and to credit any overpayments that may be required by this paper under 37 C.F.R. §§ 1.16 and 1.17 to Deposit Account No. 02-2135.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the outstanding Office Action rejections. Early and favorable action is awaited.

Respectfully submitted,

By:



Robert B. Murray  
Attorney for Applicants  
Registration No. 22,980  
ROTHWELL, FIGG, ERNST & MANBECK, P.C.  
1425 K Street, N.W., Suite 800  
Washington, D.C. 20005  
Telephone: (202)783-6040  
Facsimile: (202) 783-6031

RBM/GP:kdm

1571973\_1

US Patent Application 10/564,823

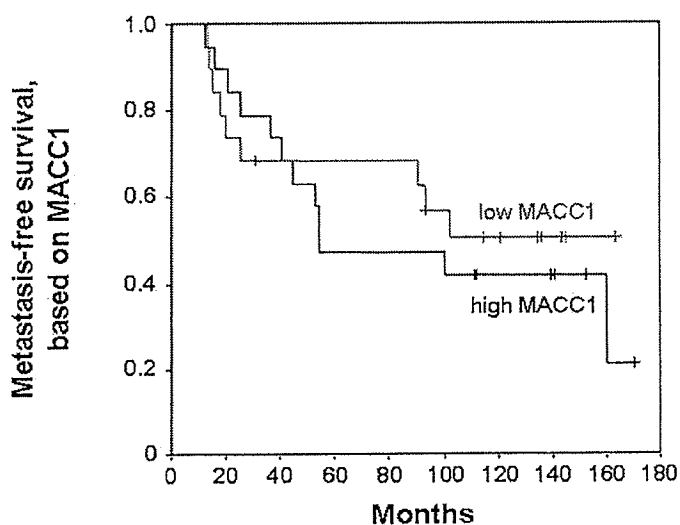
U30057US

### **MACC1 (7a5/prognostin) in breast cancer**

We analyzed 38 mammary carcinomas of stages I (3 patients), II (34 patients), and III (1 patient). Median age of the patients: 57 (range 39-75). Twenty-two patients developed distant metastases during follow-up.

Tissues were snap-frozen, serial cryo-sections/tumour were micro-dissected, RNA was isolated from tumour cell populations and quality-checked. Quantitative RT-PCR for MACC1 was performed as described previously.

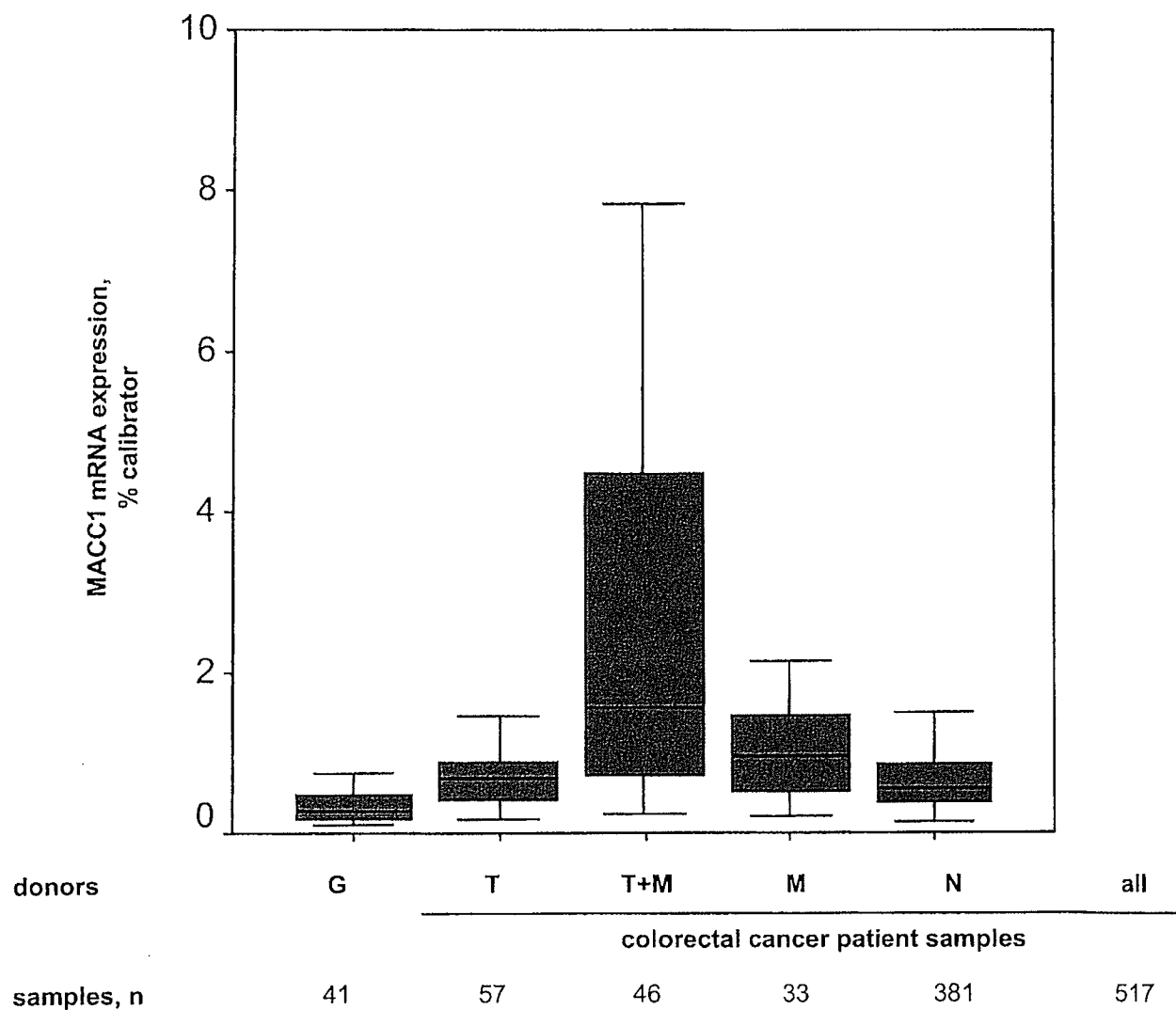
MACC1 was found to be expressed in all primary breast tumours. It was furthermore found that low (below cut off) MACC1 expression in the primary, not yet metastasized tumour might be associated with a more advantageous metastasis-free survival, whereas a high MACC1 expression in the primary tumour indicates a high probability that the primary tumour will metastasize etc. (see Figure below).



These results show the suitability of MACC1 as prognostic marker for disease progression (metastasising) and metastasis-free survival of breast cancer.

However, so far correlations of metastasis-free survival and gene expression of MACC1 were found not to be significant, which is likely due to the relatively small cohort of patients.

In summary, the expression of MACC1 is (a) higher in the malignant tissues (primary tumours) than in the corresponding healthy tissues, and (b) higher in the primary tumours, which have already undergone metastatic spread or will show manifest metastatic spread in the course of the disease than in the primary tumours showing no metastasising behaviour, which shows that MACC1 is a diagnostic as well as a prognostic marker of breast cancer.



#### Donors

H	healthy volunteers
T	tumour
T+M	tumor with synchronous metastasis (first diagnosis)
M	metachronous metastasis (first diagnosis)
N	Nachsorge (Follow-up)

### **MACC1 (7a5/prognostin) in colorectal cancer**

Circulating nucleic acids, and in particular cell-free mRNA can be detected in plasma and permits plasma-based expression profiling. The quantitative detection of tumor-derived transcripts in blood might allow the identification of occult tumors in apparently healthy people. Moreover, blood-based diagnostics are not only useful for “snap-shots”, like tumor marker determination in patients biopsies, but allow monitoring of therapy efficacy and response.

Here we provide a non-invasive, reliable, and simple blood-based assay for colorectal cancer (colon cancer and rectum cancer), by transcript quantification of the metastasis-promoting gene MACC1. We demonstrate its applicability for identification of occult tumors and/or metastasis in healthy populations and in newly diagnosed or already treated patients; as well as for identification of disease stage.

Please see the Figure.

H      healthy volunteers

T      tumor

T+M   tumor with synchronous metastasis (first diagnosis)

M      metachronous metastasis (first diagnosis)

N,      Nachsorge (Follow up)